Title

Circadian clock and stress interactions in the molecular biology of psychiatric disorders.

Journal

Current psychiatry reports, 16(10)

ISSN

1523-3812

Authors

Landgraf, Dominic
McCarthy, Michael J
Welsh, David K

Publication Date

2014-10-01

DOI

10.1007/s11920-014-0483-7

Peer reviewed

Circadian clock and stress interactions in the molecular biology of psychiatric disorders

Dominic Landgraf[1,2,*], Michael J. McCarthy[1,2,*], and David K. Welsh[1,2,#]

[1]Veterans Affairs San Diego Healthcare System, San Diego, CA

[2]Department of Psychiatry, and Center for Circadian Biology, University of California, San Diego, La Jolla, CA

*These authors contributed equally to this work.

[#]Corresponding author: David K. Welsh, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive MC-0603, La Jolla, CA 92093-0603; e-mail: welshdk@ucsd.edu.

Keywords: Circadian clock, stress, attention deficit hyperactivity disorder, alcohol use disorder, bipolar disorder, major depressive disorder, post-traumatic stress disorder, schizophrenia,

Abstract

Many psychiatric disorders are characterized by circadian rhythm abnormalities including disturbed sleep/wake cycles, changes in locomotor activity, and abnormal endocrine function. Animal models with mutations in circadian "clock genes" commonly show disturbances in reward processing, locomotor activity and novelty seeking behaviors, further supporting the idea of a connection between the circadian clock and psychiatric disorders. However, if circadian clock dysfunction is a common risk factor for multiple psychiatric disorders, it is unknown if and how these putative clock abnormalities could be expressed differently, and contribute to multiple, distinct phenotypes. One possible explanation is that the circadian clock modulates the biological responses to stressful environmental factors that vary with an individual's experience. It is known that the circadian clock and the stress response systems are closely related: Circadian clock genes regulate the physiological sensitivity to, and rhythmic release of glucocorticoids (GC). In turn, GCs have reciprocal effects on the clock. Since stressful life events or increased vulnerability to stress are risk factors for multiple psychiatric disorders including post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), alcohol use disorder (AUD) and schizophrenia (SCZ), we propose that modulation of the stress response is a common mechanism by which circadian clock genes affect these illnesses. Presently, we review how molecular components of the circadian clock may contribute to these six psychiatric disorders, and present the hypothesis that modulation of the stress response may constitute a common mechanism by which the circadian clock affects multiple psychiatric disorders.

Introduction to Circadian Clocks

Circadian clocks have evolved to anticipate daily recurring environmental changes evoked by the 24 hr rotation of the earth around its axis. In mammals, circadian clocks are entrained to the environment by light and other secondary z*eitgebers* (German: "time giver") [1]. The hypothalamic suprachiasmatic nucleus (SCN) is the master circadian clock, receiving light input directly from non-image-forming melanopsin-containing photoreceptors in retina, and regulating secondary oscillators in other brain regions and peripheral organs [2, 3]. At the molecular level, circadian clocks are based on autoregulatory transcriptional–translational feedback loops (TTL) that regulate rhythmic expression of ~20 core clock genes. The core TTL consist of the transcriptional activators BMAL1 (ARNTL), CLOCK, and NPAS2, and transcriptional repressors CRY1/2 and PER1/2/3, which inhibit their own rhythmic expression via delayed negative feedback on BMAL1/CLOCK/NPAS2 [4, 5]. A secondary loop in which RORA/B/C activate and REV-ERBα/β inhibit activity has also been described. In each case, progressive degradation of repressor proteins disinhibits activator elements. One cycle of activation and repression is completed in ~24 hours and then starts anew. In addition to maintaining the TTL, core clock genes regulate the expression of clock-controlled genes that are rhythmically expressed in organ-specific physiological processes such as neurotransmission, immune processes, metabolism and endocrine signaling.

Clocks and Psychiatric Disorders

Disturbed circadian rhythms have been associated with disrupted brain function, and multiple lines of evidence support the idea that the circadian clock is vulnerable and/or disturbed in a variety of mental illnesses including ADHD, AUD, BD, MDD, PTSD and SCZ [6]. In clinical observations, many psychiatric patients suffer altered sleep/wake cycles and show disturbed rhythms in daily functions like appetite and cognition. Conversely, disturbed rhythms in otherwise healthy individuals exposed to shift-work and jet lag may lead to deteriorating mental health, underscoring the bidirectional relationships between the circadian clock and behavior, mood and cognition [7, 8]. In animal models, mutating clock genes or manipulating light/dark cycles alters affective, locomotor and behavioral phenotypes [9], demonstrating the direct connection between clock genes and brain functions relevant to psychiatric illness. However, one challenge to the hypothesis that clock genes modulate mental illness is the fact that several clock genes have been implicated across multiple psychiatric disorders, each with distinct symptoms and phenotypic presentations. How can these different phenotypes be explained through variation in the same gene or set of genes with overlapping functions?

Stress and Psychiatric Disorders

Early life stress (including infection, trauma, neglect and abuse) is a common risk factor for a variety of mental illnesses, even those typically considered strongly heritable and genetically influenced like ADHD, BD, and SCZ [10-13]. The GCs cortisol (in humans) and corticosterone (in rodents) play major roles in the response to stress. GCs are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In response to signals from the limbic system, the paraventricular nucleus releases corticotropin-releasing hormone (CRH), signaling the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH from the pituitary signals the adrenal gland where it stimulates GC synthesis and release into the systemic circulation to alter gene expression and physiology throughout the body. In healthy subjects, the

increase of GC in response to acute stress leads to increased alertness, mobilization of glucose and fatty acids, and enhanced memory formation [14-16]. However, after chronic stress and long term elevations of GCs, the effects of GCs are detrimental with neurotoxic, immunosuppressive, and metabolic consequences [17-19]. Accordingly, many neuropsychiatric disorders are associated with abnormalities in the HPA axis, with chronically elevated cortisol and reduced sensitivity to GC [20], suggesting stress may contribute to their development. Experiments in rats have shown that rats exposed to early life stress show elevated GCs as adults [21]. Similar observations have been made in human subjects who show chronically elevated GCs and altered stress response long after a traumatic event [17]. The effects of stress can therefore be persistent, lasting long after termination of the stressor.

Connections between the Clock and Stress Response

Since disturbed circadian rhythms and altered stress responses are involved across many psychiatric conditions, it may be that an individual's genetic and environmental risk factors for a particular illness are subject to modulation by the combined actions of the circadian and stress response systems. In this way, specific illness factors (e.g. uniquely predisposing to ADHD, SCZ or AUD) are processed by a system of generalized responses (the dual actions of the clock and stress response systems) to determine specific features of the expressed phenotype(s) (Figure 1). In support of this hypothesis, the circadian clock and the stress response system are closely connected (Figure 2). Many clock gene promoters contain GC responsive elements (GREs), and GCs synchronize peripheral and central circadian oscillators [22]. For example, GCs activate the transcription of *Per* genes and are important for adapting sleep/wake rhythms to changes of environmental conditions like shift work, jet lag or irregular mealtimes [23, 24].

Conversely, it is well established that the HPA/GC system is temporally gated by the circadian clock [25]. Under physiological conditions, GC release follows a circadian rhythm, in which GC levels are highest at the beginning of the active phase and lowest at the start of the inactive phase. In the adrenal, the availability of the steroid precursor cholesterol, the storage of cholesterol and the activity of steroidogenic enzymes all show circadian rhythms [26]. At the protein level, BMAL1/CLOCK complexes interact with the glucocorticoid receptor (GR), modulating GR sensitivity in a circadian fashion, through acetylation of the GR by CLOCK during the day [27]. Accordingly, *Bmal1*$^{-/-}$ mice suffer from low CORT levels, reduced CORT sensitivity and a disturbed stress response [28]. In the negative limb of the TTL, cells from CRY1/2 double null mutant animals are more sensitive to dexamethasone regulation of target genes compared to wild type cells [29], and PER1 null mutants have increased GC levels [30]. Many stress-inducible genes are also under control of the circadian clock. We conducted an analysis of the convergence of genes containing a GR-occupied GRE [31] with those that are pervasively rhythmic in expression [32], and found that ~16% of pervasively rhythmic genes contain validated GREs in their promoters. Considering that GREs were validated in only a single tissue, and only pervasively rhythmic genes were considered, this count is likely to be a lower bound estimate of circadian clock–GC overlap.

Stress, Clock-controlled Genes, and the Central Nervous System

Many brain functions relevant to psychiatric illness are controlled simultaneously by the circadian clock and stress response systems. For example, CLOCK/BMAL1 regulates the expression of tyrosine hydroxylase (TH), the rate limiting enzyme in monoamine (dopamine, epinephrine, and norepinephrine) synthesis. TH expression is also controlled by GRs, and repeated or chronic stress is associated with increased TH expression. Elsewhere in the dopamine system, the sensitivity of dopamine receptors is regulated by the circadian clock, where elevated CRF [33] or manipulations of the GR [34] affect the sensitivity of dopamine-dependent reward pathways. The balance between excitatory (glutamate) and inhibitory (γ-amino-butyric acid, GABA) signaling is also influenced simultaneously by the circadian clock and stress systems. *Per2*$^{Brdm1-/-}$ mice show decreased levels of the Eaat1 glutamate transporter, which leads to elevated extracellular glutamate levels [35] , whereas pregnenolone, a precursor of GC that is stimulated by ACTH, acts as an NMDA receptor antagonist, and has anti-depressant activity in animals [36]. GABA levels oscillate in mood-regulating brain areas like the nucleus accumbens and is also involved in stabilizing circadian rhythms in the SCN, where it acts as an inhibitory neurotransmitter at night and as an excitatory neurotransmitter during the day [37-39]. Furthermore, GABA release is facilitated by the GCs [40]. Thus, the circadian clock and the stress response systems overlap extensively, and regulate a multitude of systems that govern affect, reward processing, locomotion and cognition. These overlapping systems may work in a coordinated manner to regulate the molecular brain mechanisms that fail in psychiatric illness. In the following sections we review six stress related psychiatric conditions, and highlight their connections to the molecular circadian clock and stress.

Post-Traumatic Stress Disorder (PTSD)

Exposure to traumatic stress can have long lasting effects on anxiety, arousal and mood. PTSD is recognized as a distinct clinical phenomenon resulting from the experience of an intense trauma, resulting in distressing re-experiencing of the event, avoidance of associated stimuli, and hyperarousal in affected individuals. While PTSD requires an environmental insult, only a fraction of subjects (10-25%) exposed to trauma develop PTSD; thus, vulnerability to PTSD has a genetic component that may include circadian clock genes. Elevated GC levels are neurotoxic, particularly to the hippocampus [18], a brain region implicated in PTSD [18, 41]. Therefore circadian dysregulation of GCs regulated by clock gene variants could affect vulnerability to PTSD by disrupting the interface between the clock and GCs in brain regions that are vulnerable to stress. In animal models, there is preliminary support for cross talk between the clock and stress systems influencing fear conditioning (a model for PTSD), in that experimental jet lag increases susceptibility to fear conditioning and potentiates corticosterone release in mice [42].

In humans, genetic studies offer further support for a circadian component to stress vulnerability and PTSD. One gene of particular interest is FKBP5, a chaperone protein involved in directing activated GRs to the nucleus. FKBP5 is rhythmically expressed in most tissues [32], suggesting that this protein is involved in circadian gating of GC signals. FKBP5 has been implicated in a number of stress related psychiatric disorders, including psychological stress in children [43, 44], dimensional stress in healthy subjects [45], MDD [46], and PTSD [47]. Two core clock genes have been implicated in genome-wide association studies (GWAS) of PTSD: *PACAP* and *RORA*. PACAP (pituitary adenylate cyclase-activating polypeptide) affects the central SCN clock, and is involved in phase resetting in response to light [48].

ADCYAP1, the gene encoding PACAP, is associated with PTSD selectively in females [49, 50]. The same *ADCYAP1* variant is associated with increased reactivity to fear in the amygdala and hippocampus among previously traumatized females [51]. Interestingly, the PACAP receptor, VIPR2, has been implicated in SCZ (see below). RORA is rhythmically expressed and regulates BMAL activity. RORA was first identified as a PTSD risk gene in a cohort of combat veterans [52], and subsequently replicated in a cohort of hurricane survivors experiencing psychological distress [53]. However, RORA may demonstrate the broad-reaching influence of the clock across psychiatric disorders, having also been implicated in anti-depressant response [54], BD [55], dimensional depression [56], autism [57], ADHD and SCZ [58].

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a disorder of impulse control, inattention and hyperactivity associated with inappropriate night time activity and insomnia. The disorder is strongly heritable, with about 80% of variance explained by genetic factors, but stress, especially childhood trauma, is an environmental risk factor [11, 12]. Accordingly, family studies point to shared susceptibility factors between ADHD and PTSD [59]. Classically, ADHD was described as a childhood disorder, but it is now recognized that age of onset may extend into adolescence [60], and that symptoms persist into adulthood in about 65% of subjects [61]. Of interest, the incidence of ADHD varies geographically in association with light exposure [62], with regions exposed to low levels of light having higher rates of ADHD. While this provocative finding requires further study, it reinforces the idea that ADHD may involve the circadian clock and/or be related to photic inputs. Candidate gene studies suggest that ADHD and dimensional inattention may be associated with the CLOCK -3111T/C variant genotype [63-65]. While clock gene variants are not among the strongest associations with ADHD found by GWAS, clock gene variants may be enriched among weaker GWAS associations [58]. A gene expression study from subjects with adult ADHD revealed a number of alterations in molecular rhythms [66], including loss of BMAL and PER2 expression rhythms in oral mucosal cells, blunted melatonin rhythms, and 3 hr phase delays in cortisol rhythms relative to controls. Consistent with previous behavioral reports, the same study also found high levels of activity at night, greater evening preference, and long latency to sleep onset. While the molecular basis of rhythm abnormalities in humans with ADHD remains unclear, a mouse model of ADHD has been developed by forebrain-specific deletion of the gene encoding casein kinase 1 delta [67]. This animal is hyperactive, has deficits in nesting behaviors, and shows the same paradoxically lower levels of locomotor activity in response to amphetamines as shown by ADHD patients. Another therapeutic agent for ADHD, atomoxetine, has phase-dependent effects on the central SCN clock and amplifies the phase response to light in mice [68].

Schizophrenia (SCZ)

SCZ is a neurodevelopmental psychotic disorder characterized by hallucinations, disorganized thought, and cognitive impairment, resulting in chronic and severe social and occupational dysfunction. SCZ is heritable, with 80% of variance explained by genetic factors. However, stressful environmental risk factors like prenatal exposure to infection [69], malnutrition [70] and immigration [71] have also been identified. Among the symptoms of SCZ, circadian rhythm abnormalities have been observed, with impaired onset of evening melatonin release, disorganized sleep, and perturbed activity rhythms.

Candidate gene studies implicated a number of clock genes in SCZ, but replication in larger patient samples by GWAS has been largely unsuccessful. One report found an enrichment of clock gene single nucleotide polymorphisms (SNPs) among those weakly associated with SCZ [58]. However, subsequent set-based analyses using the larger PGC GWAS data set and more conservative assumptions revealed no such enrichment [72]. While over 100 SNPs have now been strongly associated with SCZ [73], none directly implicate the circadian clock. However, several are located within genes with pleiotropic effects that may affect clock function. As an example, *CACNA1C* encodes an L-type calcium channel subunit, and is strongly associated with not just SCZ but also two other disorders with circadian features: BD [74] and primary insomnia [75]. In the SCN, calcium is rhythmic and required for the rhythmic expression of clock genes [76, 77]; and L-type calcium channel antagonists attenuate rhythms in neurons [76]. Hence, circadian rhythms might be disrupted in psychiatric disorders via aberrant calcium signaling.

Copy number variant (CNV) studies have identified a number of chromosomal duplications/deletions strongly associated with SCZ susceptibility [78]. While these CNVs are individually rare, and account for only a small minority (<1%) of SCZ cases, they are associated with large effect sizes (odds ratios as high as 60), suggesting some CNVs may be causative factors in SCZ. In contrast to GWAS, CNV studies have directly implicated the clock in SCZ, namely by a SCZ-associated duplication in chromosome 7q36 affecting *VIPR2*, the gene encoding the receptor for vasoactive intestinal peptide receptor 2 (VIPR2) [79]. VIPR2 binds vasoactive intestinal peptide (VIP) and PACAP. VIP is involved in neuronal coupling in the SCN and has been implicated in the phase resetting response to light [80]. Behavioral activity of the *VIPR2* null mutant mouse is arrhythmic in constant darkness and shifts more rapidly in response to shifts of the light/dark cycle [81]. However, neither null nor duplication *VIPR2* mutants have been assessed as animal models for SCZ, so the connection between biological timing and SCZ-related cognitive function remains unclear.

Major Depressive Disorder (MDD) and Bipolar Disorder (BD)

MDD and BD are heritable mood disorders (with MDD ~37%, and BD ~85% of variance attributable to genetics) characterized by episodes of depression only (MDD) or depression and mania (BD) [82, 83]. Circadian rhythm abnormalities, including disturbed sleep, diurnal mood variation, changes in appetite, and social interaction, are characteristic symptoms of both BD and MDD [84, 85, 58]. A further hallmark of MDD and BD is a disturbance of HPA axis activity associated with elevated GC and CRH levels, failure of dexamethasone to suppress GC, and reduced GC sensitivity [86, 87]. Depression can be precipitated when circadian rhythms are disturbed by environmental conditions as in shift-work, jet lag and sleep deprivation. Disrupted activity cycles are an important cause of mood relapses in BD [7]. Therapies for depression have been developed that directly target the circadian clock, including light exposure, melatonergic drugs, and shifting of sleep/wake schedules [88-92].

Candidate gene studies have identified a number of clock gene variants associated with MDD or BD, including *BMAL1 (ARNTL1)*, *CLOCK*, *NPAS2*, *PER3*, *CRY1*, *RORA* and *TIMELESS* [93-95], but only RORA has been supported in more powerful GWAS [55, 54, 56]. In GWAS, an enrichment for clock gene SNPs was found among variants weakly associated with BD and MDD [58]. While a subsequent analysis using

larger data sets and more conservative assumptions failed to detect an enrichment of clock gene SNPs, certain clock genes were still implicated in the larger analysis, including DBP1 and DEC2 (BHLHB3) in BD, and REV-ERBα (NR1D1) in MDD [72].

A recent human postmortem study showed that in healthy control subjects, *BMAL1* (*ARNTL1)*, *PER1-3*, *DEC1/2*, *REV-ERBα* , and *DBP1* are rhythmically expressed in brain regions involved in mood regulation, but these rhythms are attenuated in subjects with MDD [96]. Although these data do not discriminate between weaker clock gene rhythms in individual MDD subjects and greater variability in phase across subjects [9], they do establish that the molecular machinery of brain circadian clocks is affected in MDD. Another approach to human studies is the investigation of rhythms in cells from patients. Since the molecular circadian machinery is similar across cell types, the rhythms of skin fibroblasts mirror those in other cells from an individual. Importantly, this method allows the researcher to investigate rhythms longitudinally in an individual subject, rather than conducting group analyses across subjects. Using this approach, a recent study revealed that fibroblast rhythms from BD patients show longer circadian periods than rhythms from control fibroblasts and that rhythm amplitude is differentially affected by lithium in cells from BD subjects [97].

Animal studies provide further evidence of associations between clock genes and mood. Most strikingly, *Clock-Δ19* mice show features of mania, including hyperactivity, reduced sleep, increased reward seeking behavior, and more open field activity [98-100]. Therefore, *Clock-Δ19* mice have become an accepted animal model for mania, and demonstrate the potential for a single clock gene mutation to impact mood. The PER proteins may also affect mood in complex ways. $Per1^{Brdm1-/-}$ and $Per2^{Brdm1-/-}$ mutant mice show depression-like and mania-like behaviors, respectively [101], whereas $Per1^{ldc-/-}$; $Per2^{ldc-/-}$ double mutants have increased anxiety-like behavior [102]. The $Dbp^{-/-}$ mouse is hypoactive at baseline, but hyperactive when exposed to chronic stress, modeling to some extent the alternating depression-like and mania-like behavior seen in BD. Supporting the notion of clock-stress interaction, $Dbp^{-/-}$ mice appear more vulnerable to stress, gaining more weight and consuming more alcohol than similarly stressed control mice [103]. Mutations of many clock modulating factors, like casein kinase 1δ/ε (CSNK1D/E), f-box/lrr-repeat protein 3 (FBXL3), sodium potassium ATPase (ATP1A3), and glycogen synthase kinase 3B (GSK3B) also lead to mood abnormalities [9]. However, these modulators have additional cellular functions, making the connection between the observed mood-related phenotypes and the circadian clock unclear.

Alcohol Use Disorders (AUD)

Socially acceptable alcohol use is typically an evening activity, while morning alcohol intake is usually considered pathological [104]. Daily patterns of drinking behavior are strongly influenced by culture, but may also reflect fundamental, biological patterns in reward processing, and physiological responses to alcohol that were incorporated into cultural norms in response to biological pressures. Genetic studies suggest that 40-60% of the risk for developing AUD is inherited [105], but the majority of genetic risk loci remain unknown and/or poorly characterized. Therefore, some have suggested that a portion of this risk might be accounted for by genes that affect the function of the circadian clock.

Among abstinent, recovering alcoholics, persistent sleep problems are common and predict relapse [106]. Consistent with the idea that the circadian clock affects alcohol intake at earlier stages, young adults at risk for AUD commonly report disturbances in sleep [107], and a preference for evening activity (nocturnal chronotype) [108]. In a study of 537 young adults from a community sample, those with nocturnal chronotype consumed more than twice the volume of alcohol compared to those with morning or neutral chronotypes [109]. In other studies of subjects deemed high risk for AUD based upon family history, interaction of the stress system and circadian rhythms is again apparent, with daily rhythms of ACTH and cortisol showing reduced amplitudes compared to low risk subjects [110].

Daily rhythms of human alcohol consumption are recapitulated in rodent models. Rat alcohol consumption peaks at night in a light/dark cycle [111]. In mice, alcohol is more intoxicating at night than during the day, and genetic knockout of *Per2* eliminates this differential sensitivity, leading to overall increases in alcohol intake across the 24 hr cycle [112]. *Per1* mutants consume more alcohol than controls, but only following a social defeat stress [113], and *Per3* has been associated with alcohol preference and stress response in mice [114]. Mice bred for high alcohol intake have shorter free-running circadian periods [115]. Alcohol preferring rats have also have short periods and entrainment deficits in a shortening photoperiod [116].

In human studies, variants in several clock genes have been associated with various alcohol-related phenotypes: *BMAL1/2* (*ARNTL1/2)* variants are associated with alcohol dependence and alcohol intake [117]; *PER1* with alcohol consumption in adolescents and adult alcoholics [113]; *PER2* with high alcohol intake and interaction with insomnia and alcohol consumption in young males [35, 118]; and *CLOCK* with co-morbid AUD and depressive disorders [119]. Using a bioluminescent *Per2::luc* reporter to measure gene expression rhythms in human fibroblasts, a relationship between AUD severity and rhythms was found, in which the more severely affected alcoholics had shorter circadian periods, consistent with the studies of alcohol-preferring mice [120].

Conclusion

The circadian clock and the stress response system are closely interconnected and reciprocally regulated. In the context of psychiatric disorders, the interplay between circadian clocks and stress response may broadly affect the impact of environmental stressors on the brain, thereby determining functional outcomes. General responses mediated by the clock and stress systems may impact specific genetic vulnerabilities (i.e. disease-specific risk factors), leading to the expression of distinct phenotypes commonly recognized as psychiatric disorders. In this way, the same environmental stressor, or variants in the same system, could result in different psychopathologies. Since both the circadian system and the stress response system are built upon complex gene networks, the expected range of biological interactions in these networks is extremely broad, and it would be expected that there would be phenotypic overlap and/or ambiguity in the psychiatric phenotypes resulting from their dysfunction. In clinical practice, this is indeed what is observed: Many patients have atypical presentations of established disorders, there is heterogeneity in treatment response, and patients are commonly

diagnosed with more than one condition. While this explanation is by no means exhaustive, it may go some way towards explaining the multitude of psychiatric phenotypes associated with disrupted circadian rhythms. Further experimentation is needed to determine the extent to which the clock and stress systems overlap and to what extent they are independent in modulating brain functions.

Outlook

Targeting circadian clock function may modulate the impact of stress on brain function and/or treat established psychiatric illness. Bright light therapy and sleep manipulation, especially in combination, are effective in mood disorders [90], and novel pharmacological approaches may hold promise for the treatment of a wide variety of psychiatric disorders that currently lack adequate drug therapies. Indeed, it has been suggested that the mood stabilizer lithium may have a circadian mechanism of action [97], and casein kinase 1δ/ε inhibitors have shown promise in pre-clinical animal models of AUD [121] and BD [122]. Additional compounds have been developed to target the ROR/REV-ERB nuclear receptors [123], CRYs [124], melanopsin-containing photoreceptors [125] and other complex mechanisms [123] that strongly affect circadian rhythms, but remain poorly characterized with respect to brain effects and potential as treatments for psychiatric conditions. Suppression of GC synthesis with metyrapone counteracts the elevations in GC levels associated with environmental changes, and accelerates the clock's adaptation, potentially offering the means to better adjust the circadian system to stressful environments [23]. However, because many drugs targeting the GC system directly (including metyrapone) have metabolic effects that would limit their use in chronic diseases, an indirect approach towards stress modulation through the clock may have advantages compared to direct manipulation of GC synthetic pathways. While additional work is clearly needed to assess the advantages and risks of a "chronotherapeutic" approach to mental illness, this rapidly developing field holds great promise and should be explored.

Acknowledgements

This work was supported by a Veterans Affairs Merit Award (1I01BX001146) to DKW, and a VA Career Development Award (1IK2BX001275) to MJM. The funders had no role in the analysis, decision to publish, or preparation of the manuscript.

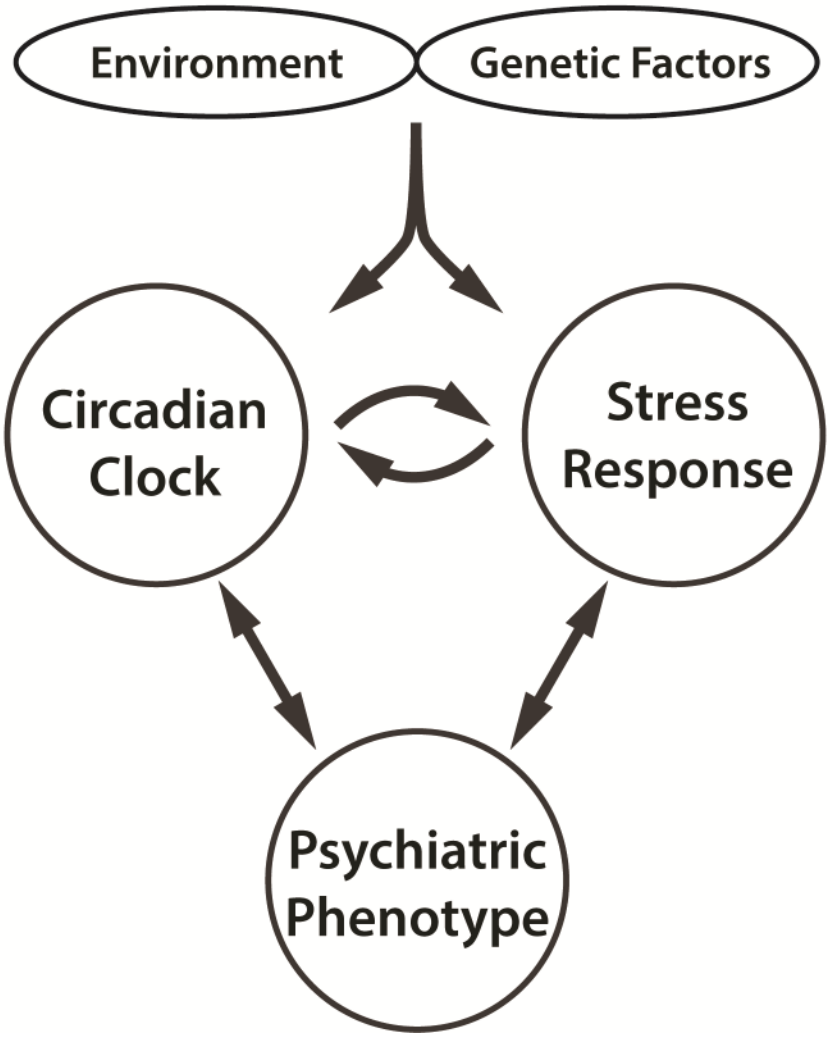

Fig. 1: Environmental and genetic factors are modulated concurrently by the dual actions of the circadian clock and the stress response system, which interact closely to regulate brain function. Conversely, the psychiatric phenotype impacts the circadian clock and the stress response system.

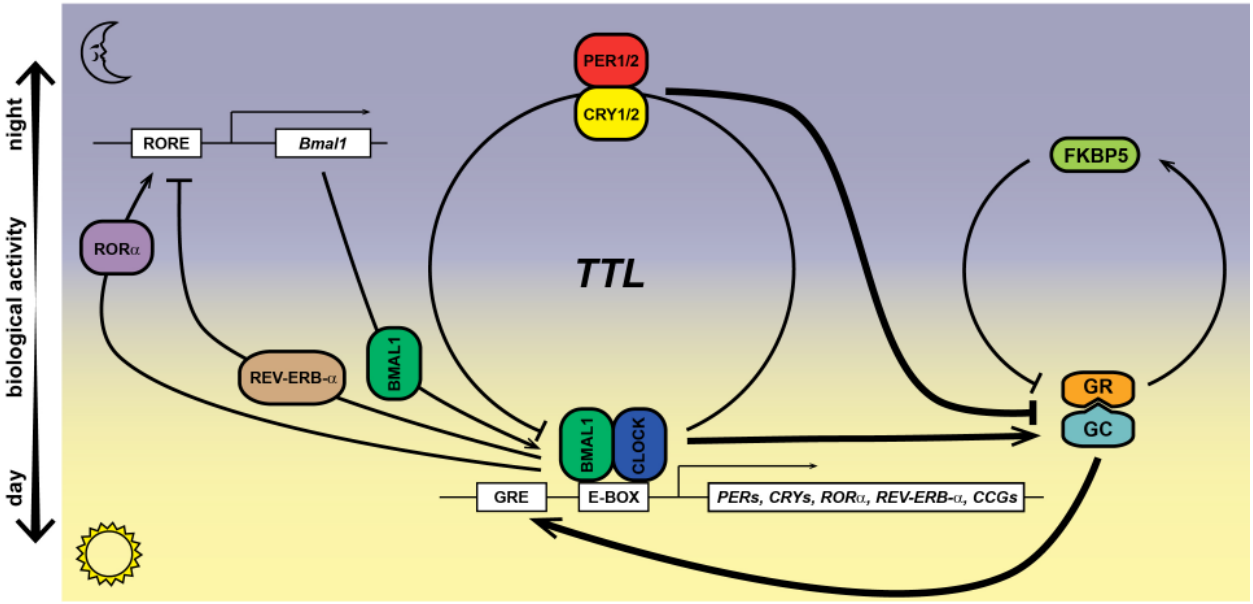

Fig. 2: The circadian clock and the stress response system interact closely. During the day BMAL1 and CLOCK proteins are expressed at high levels to activate transcription of *PERs*, *CRYs*, *RORα*, *REV-ERBα*, and *CCGs,* as well as to promote the activity of GRs which, in turn, elevate transcription of GC-inducible genes like *FKBP5*. An accessory feedback loop consists of RORα, an activator of *BMAL1* expression and REV-ERBα, an inhibitor of *BMAL1* expression. GCs facilitate the expression of GC-responsive clock genes and clock controlled genes (*CCGs)* with GRE promoter elements. At night, PER and CRY protein levels are high and repress the activity of BMAL1/CLOCK and the GR. Through feedback inhibition, FKBP5 suppresses GR activity. Due to the tight connection between the circadian clock and the stress response system, manipulations of one system naturally lead to changes in the other.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Daan S, Pittendrigh CS. A Functional analysis of circadian pacemakers in nocturnal rodents. Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology. 1976;Volume 106(Number 3):223-355.
2. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annual review of physiology. 2010;72:517-49. doi:10.1146/annurev-physiol-021909-135821.
3. Ecker JL, Dumitrescu ON, Wong KY, Alam NM, Chen SK, LeGates T et al. Melanopsin-expressing retinal ganglion-cell photoreceptors: cellular diversity and role in pattern vision. Neuron. 2010;67(1):49-60. doi:10.1016/j.neuron.2010.05.023.
4. Koike N, Yoo SH, Huang HC, Kumar V, Lee C, Kim TK et al. Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. Science. 2012;338(6105):349-54. doi:10.1126/science.1226339.
5. Lowrey PL, Takahashi JS. Genetics of circadian rhythms in Mammalian model organisms. Advances in genetics. 2011;74:175-230. doi:10.1016/B978-0-12-387690-4.00006-4.
6. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nature reviews Neuroscience. 2010;11(8):589-99. doi:10.1038/nrn2868.
7. Rosenberg R, Doghramji PP. Is shift work making your patient sick? Emerging theories and therapies for treating shift work disorder. Postgraduate medicine. 2011;123(5):106-15. doi:10.3810/pgm.2011.09.2465.
8. Katz G, Durst R, Zislin Y, Barel Y, Knobler HY. Psychiatric aspects of jet lag: review and hypothesis. Medical hypotheses. 2001;56(1):20-3. doi:10.1054/mehy.2000.1094.
9. Landgraf D, McCarthy MJ, Welsh DK. The Role of the Circadian Clock in Animal Models of Mood Disorders. Behavioral neuroscience. 2014. doi:10.1037/a0036029.
10. Carr CP, Martins CM, Stingel AM, Lemgruber VB, Juruena MF. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. The Journal of nervous and mental disease. 2013;201(12):1007-20. doi:10.1097/NMD.0000000000000049.
11. Ouyang L, Fang X, Mercy J, Perou R, Grosse SD. Attention-deficit/hyperactivity disorder symptoms and child maltreatment: a population-based study. The Journal of pediatrics. 2008;153(6):851-6. doi:10.1016/j.jpeds.2008.06.002.
12. Lara C, Fayyad J, de Graaf R, Kessler RC, Aguilar-Gaxiola S, Angermeyer M et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biological psychiatry. 2009;65(1):46-54. doi:10.1016/j.biopsych.2008.10.005.
13. Brietzke E, Kauer Sant'anna M, Jackowski A, Grassi-Oliveira R, Bucker J, Zugman A et al. Impact of childhood stress on psychopathology. Rev Bras Psiquiatr. 2012;34(4):480-8.
14. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nature reviews Neuroscience. 2005;6(6):463-75. doi:10.1038/nrn1683.
15. Lecocq FR, Mebane D, Madison LL. The Acute Effect of Hydrocortisone on Hepatic Glucose Output and Peripheral Glucose Utilization. The Journal of clinical investigation. 1964;43:237-46. doi:10.1172/JCI104908.
16. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism: clinical and experimental. 2011;60(11):1500-10. doi:10.1016/j.metabol.2011.06.012.
17. Maniam J, Antoniadis C, Morris MJ. Early-Life Stress, HPA Axis Adaptation, and Mechanisms Contributing to Later Health Outcomes. Frontiers in endocrinology. 2014;5:73. doi:10.3389/fendo.2014.00073.

18. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of general psychiatry. 2000;57(10):925-35.
19. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Molecular and cellular endocrinology. 2011;335(1):2-13. doi:10.1016/j.mce.2010.04.005.
20. Carroll BJ. The dexamethasone suppression test for melancholia. The British journal of psychiatry : the journal of mental science. 1982;140:292-304.
21. Zhang J, Abdallah CG, Chen Y, Huang T, Huang Q, Xu C et al. Behavioral deficits, abnormal corticosterone, and reduced prefrontal metabolites of adolescent rats subject to early life stress. Neuroscience letters. 2013;545:132-7. doi:10.1016/j.neulet.2013.04.035.
22. Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. Trends in endocrinology and metabolism: TEM. 2010;21(5):277-86. doi:10.1016/j.tem.2009.12.011.
23. Kiessling S, Eichele G, Oster H. Adrenal glucocorticoids have a key role in circadian resynchronization in a mouse model of jet lag. The Journal of clinical investigation. 2010;120(7):2600-9. doi:10.1172/JCI41192.
24. Le Minh N, Damiola F, Tronche F, Schutz G, Schibler U. Glucocorticoid hormones inhibit food-induced phase-shifting of peripheral circadian oscillators. The EMBO journal. 2001;20(24):7128-36. doi:10.1093/emboj/20.24.7128.
25. Kalsbeek A, van der Spek R, Lei J, Endert E, Buijs RM, Fliers E. Circadian rhythms in the hypothalamo-pituitary-adrenal (HPA) axis. Molecular and cellular endocrinology. 2012;349(1):20-9. doi:10.1016/j.mce.2011.06.042.
26. Oster H, Damerow S, Kiessling S, Jakubcakova V, Abraham D, Tian J et al. The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. Cell metabolism. 2006;4(2):163-73. doi:10.1016/j.cmet.2006.07.002.
27. Charmandari E, Chrousos GP, Lambrou GI, Pavlaki A, Koide H, Ng SS et al. Peripheral CLOCK regulates target-tissue glucocorticoid receptor transcriptional activity in a circadian fashion in man. PloS one. 2011;6(9):e25612. doi:10.1371/journal.pone.0025612.
28. Leliavski A, Shostak A, Husse J, Oster H. Impaired glucocorticoid production and response to stress in Arntl-deficient male mice. Endocrinology. 2014;155(1):133-42. doi:10.1210/en.2013-1531.
29. Lamia KA, Papp SJ, Yu RT, Barish GD, Uhlenhaut NH, Jonker JW et al. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. Nature. 2011;480(7378):552-6. doi:10.1038/nature10700.
30. Dallmann R, Touma C, Palme R, Albrecht U, Steinlechner S. Impaired daily glucocorticoid rhythm in Per1 (Brd) mice. Journal of comparative physiology A, Neuroethology, sensory, neural, and behavioral physiology. 2006;192(7):769-75. doi:10.1007/s00359-006-0114-9.
31. Reddy TE, Pauli F, Sprouse RO, Neff NF, Newberry KM, Garabedian MJ et al. Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. Genome research. 2009;19(12):2163-71. doi:10.1101/gr.097022.109.
32. Yan J, Wang H, Liu Y, Shao C. Analysis of gene regulatory networks in the mammalian circadian rhythm. PLoS computational biology. 2008;4(10):e1000193. doi:10.1371/journal.pcbi.1000193.
33. Boyson CO, Holly EN, Shimamoto A, Albrechet-Souza L, Weiner LA, Debold JF et al. Social Stress and CRF-Dopamine Interactions in the VTA: Role in Long-Term Escalation of Cocaine Self-Administration. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2014;34(19):6659-67. doi:10.1523/JNEUROSCI.3942-13.2014.
34. Parnaudeau S, Dongelmans ML, Turiault M, Ambroggi F, Delbes AS, Cansell C et al. Glucocorticoid receptor gene inactivation in dopamine-innervated areas selectively decreases behavioral responses to amphetamine. Frontiers in behavioral neuroscience. 2014;8:35. doi:10.3389/fnbeh.2014.00035.
35. Spanagel R, Pendyala G, Abarca C, Zghoul T, Sanchis-Segura C, Magnone MC et al. The clock gene Per2 influences the glutamatergic system and modulates alcohol consumption. Nature medicine. 2005;11(1):35-42. doi:10.1038/nm1163.
36. Holubova K, Nekovarova T, Pistovcakova J, Sulcova A, Stuchlik A, Vales K. Pregnanolone Glutamate, a Novel Use-Dependent NMDA Receptor Inhibitor, Exerts Antidepressant-Like Properties in Animal Models. Frontiers in behavioral neuroscience. 2014;8:130. doi:10.3389/fnbeh.2014.00130.

37. Castaneda TR, de Prado BM, Prieto D, Mora F. Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light. Journal of pineal research. 2004;36(3):177-85.
38. Wagner S, Castel M, Gainer H, Yarom Y. GABA in the mammalian suprachiasmatic nucleus and its role in diurnal rhythmicity. Nature. 1997;387(6633):598-603. doi:10.1038/42468.
39. Liu C, Reppert SM. GABA synchronizes clock cells within the suprachiasmatic circadian clock. Neuron. 2000;25(1):123-8.
40. Di S, Maxson MM, Franco A, Tasker JG. Glucocorticoids regulate glutamate and GABA synapse-specific retrograde transmission via divergent nongenomic signaling pathways. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009;29(2):393-401. doi:10.1523/JNEUROSCI.4546-08.2009.
41. Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. Journal of affective disorders. 2005;88(1):79-86. doi:10.1016/j.jad.2005.05.014.
42. Loh DH, Navarro J, Hagopian A, Wang LM, Deboer T, Colwell CS. Rapid changes in the light/dark cycle disrupt memory of conditioned fear in mice. PloS one. 2010;5(9). doi:10.1371/journal.pone.0012546.
43. Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, Miller A et al. Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. Molecular psychiatry. 2005;10(12):1058-9. doi:10.1038/sj.mp.4001727.
44. Roy A, Gorodetsky E, Yuan Q, Goldman D, Enoch MA. Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2010;35(8):1674-83. doi:10.1038/npp.2009.236.
45. Ising M, Depping AM, Siebertz A, Lucae S, Unschuld PG, Kloiber S et al. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. The European journal of neuroscience. 2008;28(2):389-98. doi:10.1111/j.1460-9568.2008.06332.x.
46. Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Putz B et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nature genetics. 2004;36(12):1319-25. doi:10.1038/ng1479.
47. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA : the journal of the American Medical Association. 2008;299(11):1291-305. doi:10.1001/jama.299.11.1291.
48. Colwell CS, Michel S, Itri J, Rodriguez W, Tam J, Lelievre V et al. Selective deficits in the circadian light response in mice lacking PACAP. American journal of physiology Regulatory, integrative and comparative physiology. 2004;287(5):R1194-201. doi:10.1152/ajpregu.00268.2004.
49. Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011;470(7335):492-7. doi:10.1038/nature09856.
50. Almli LM, Mercer KB, Kerley K, Feng H, Bradley B, Conneely KN et al. ADCYAP1R1 genotype associates with post-traumatic stress symptoms in highly traumatized African-American females. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2013;162B(3):262-72. doi:10.1002/ajmg.b.32145.
51. Stevens JS, Almli LM, Fani N, Gutman DA, Bradley B, Norrholm SD et al. PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(8):3158-63. doi:10.1073/pnas.1318954111.
52. Logue MW, Baldwin C, Guffanti G, Melista E, Wolf EJ, Reardon AF et al. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Molecular psychiatry. 2013;18(8):937-42. doi:10.1038/mp.2012.113.
53. Amstadter AB, Sumner JA, Acierno R, Ruggiero KJ, Koenen KC, Kilpatrick DG et al. Support for association of RORA variant and post traumatic stress symptoms in a population-based study of hurricane exposed adults. Molecular psychiatry. 2013;18(11):1148-9. doi:10.1038/mp.2012.189.

54. Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD et al. A genomewide association study of citalopram response in major depressive disorder. Biological psychiatry. 2010;67(2):133-8. doi:10.1016/j.biopsych.2009.08.029.
55. Smith EN, Bloss CS, Badner JA, Barrett T, Belmonte PL, Berrettini W et al. Genome-wide association study of bipolar disorder in European American and African American individuals. Molecular psychiatry. 2009;14(8):755-63. doi:10.1038/mp.2009.43.
56. Terracciano A, Tanaka T, Sutin AR, Sanna S, Deiana B, Lai S et al. Genome-wide association scan of trait depression. Biological psychiatry. 2010;68(9):811-7. doi:10.1016/j.biopsych.2010.06.030.
57. Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2010;24(8):3036-51. doi:10.1096/fj.10-154484.
58. McCarthy MJ, Nievergelt CM, Kelsoe JR, Welsh DK. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. PloS one. 2012;7(2):e32091. doi:10.1371/journal.pone.0032091.
59. Antshel KM, Kaul P, Biederman J, Spencer TJ, Hier BO, Hendricks K et al. Posttraumatic stress disorder in adult attention-deficit/hyperactivity disorder: clinical features and familial transmission. The Journal of clinical psychiatry. 2013;74(3):e197-204. doi:10.4088/JCP.12m07698.
60. Peyre H, Hoertel N, Cortese S, Acquaviva E, De Maricourt P, Limosin F et al. Attention-deficit/hyperactivity disorder symptom expression: a comparison of individual age at onset using item response theory. The Journal of clinical psychiatry. 2014;75(4):386-92. doi:10.4088/JCP.13m08638.
61. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychological medicine. 2006;36(2):159-65. doi:10.1017/S003329170500471X.
62. Arns M, van der Heijden KB, Arnold LE, Kenemans JL. Geographic variation in the prevalence of attention-deficit/hyperactivity disorder: the sunny perspective. Biological psychiatry. 2013;74(8):585-90. doi:10.1016/j.biopsych.2013.02.010.
63. Kissling C, Retz W, Wiemann S, Coogan AN, Clement RM, Hunnerkopf R et al. A polymorphism at the 3'-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2008;147(3):333-8. doi:10.1002/ajmg.b.30602.
64. Xu X, Breen G, Chen CK, Huang YS, Wu YY, Asherson P. Association study between a polymorphism at the 3'-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. Behavioral and brain functions : BBF. 2010;6:48. doi:10.1186/1744-9081-6-48.
65. Jeong SH, Yu JC, Lee CH, Choi KS, Choi JE, Kim SH et al. Human CLOCK gene-associated attention deficit hyperactivity disorder-related features in healthy adults: quantitative association study using Wender Utah Rating Scale. European archives of psychiatry and clinical neuroscience. 2014;264(1):71-81. doi:10.1007/s00406-013-0443-y.
66. Baird AL, Coogan AN, Siddiqui A, Donev RM, Thome J. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. Molecular psychiatry. 2012;17(10):988-95. doi:10.1038/mp.2011.149.
67. Zhou M, Rebholz H, Brocia C, Warner-Schmidt JL, Fienberg AA, Nairn AC et al. Forebrain overexpression of CK1delta leads to down-regulation of dopamine receptors and altered locomotor activity reminiscent of ADHD. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(9):4401-6. doi:10.1073/pnas.0915173107.
68. O'Keeffe SM, Thome J, Coogan AN. The noradrenaline reuptake inhibitor atomoxetine phase-shifts the circadian clock in mice. Neuroscience. 2012;201:219-30. doi:10.1016/j.neuroscience.2011.11.002.
69. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. The American journal of psychiatry. 2010;167(3):261-80. doi:10.1176/appi.ajp.2009.09030361.
70. Susser E, St Clair D, He L. Latent effects of prenatal malnutrition on adult health: the example of schizophrenia. Annals of the New York Academy of Sciences. 2008;1136:185-92. doi:10.1196/annals.1425.024.
71. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. The American journal of psychiatry. 2005;162(1):12-24. doi:10.1176/appi.ajp.162.1.12.

72. Byrne EM, Heath AC, Madden PA, Pergadia ML, Hickie IB, Montgomery GW et al. Testing the role of circadian genes in conferring risk for psychiatric disorders. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2014;165B(3):254-60. doi:10.1002/ajmg.b.32230.
73. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;advance online publication. doi:10.1038/nature13595.
74. Green EK, Hamshere M, Forty L, Gordon-Smith K, Fraser C, Russell E et al. Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case-control sample. Molecular psychiatry. 2013;18(12):1302-7. doi:10.1038/mp.2012.142.
75. Byrne EM, Gehrman PR, Medland SE, Nyholt DR, Heath AC, Madden PA et al. A genome-wide association study of sleep habits and insomnia. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2013;162B(5):439-51. doi:10.1002/ajmg.b.32168.
76. Colwell CS. Circadian modulation of calcium levels in cells in the suprachiasmatic nucleus. The European journal of neuroscience. 2000;12(2):571-6.
77. Lundkvist GB, Kwak Y, Davis EK, Tei H, Block GD. A calcium flux is required for circadian rhythm generation in mammalian pacemaker neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2005;25(33):7682-6. doi:10.1523/JNEUROSCI.2211-05.2005.
78. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. Cell. 2012;148(6):1223-41. doi:10.1016/j.cell.2012.02.039.
79. Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A et al. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. Nature. 2011;471(7339):499-503. doi:10.1038/nature09884.
80. Evans JA, Leise TL, Castanon-Cervantes O, Davidson AJ. Dynamic interactions mediated by nonredundant signaling mechanisms couple circadian clock neurons. Neuron. 2013;80(4):973-83. doi:10.1016/j.neuron.2013.08.022.
81. Harmar AJ. An essential role for peptidergic signalling in the control of circadian rhythms in the suprachiasmatic nuclei. Journal of neuroendocrinology. 2003;15(4):335-8.
82. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. The American journal of psychiatry. 2000;157(10):1552-62.
83. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Archives of general psychiatry. 2003;60(5):497-502. doi:10.1001/archpsyc.60.5.497.
84. McClung CA. Circadian genes, rhythms and the biology of mood disorders. Pharmacology & therapeutics. 2007;114(2):222-32. doi:10.1016/j.pharmthera.2007.02.003.
85. Boyce P, Barriball E. Circadian rhythms and depression. Australian family physician. 2010;39(5):307-10.
86. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. Progress in neuro-psychopharmacology & biological psychiatry. 2011;35(3):722-9. doi:10.1016/j.pnpbp.2010.04.011.
87. Daban C, Vieta E, Mackin P, Young AH. Hypothalamic-pituitary-adrenal axis and bipolar disorder. The Psychiatric clinics of North America. 2005;28(2):469-80. doi:10.1016/j.psc.2005.01.005.
88. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N et al. Bright-light therapy in the treatment of mood disorders. Neuropsychobiology. 2011;64(3):152-62. doi:10.1159/000328950.
89. Lewy AJ, Rough JN, Songer JB, Mishra N, Yuhas K, Emens JS. The phase shift hypothesis for the circadian component of winter depression. Dialogues in clinical neuroscience. 2007;9(3):291-300.
90. Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biological psychiatry. 2009;66(3):298-301. doi:10.1016/j.biopsych.2009.02.018.
91. Di Giannantonio M, Martinotti G. Anhedonia and major depression: the role of agomelatine. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2012;22 Suppl 3:S505-10. doi:10.1016/j.euroneuro.2012.07.004.

92. Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M et al. Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatric disease and treatment. 2013;9:243-51. doi:10.2147/NDT.S41557.
93. Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2003;123B(1):23-6. doi:10.1002/ajmg.b.20038.
94. Soria V, Martinez-Amoros E, Escaramis G, Valero J, Perez-Egea R, Garcia C et al. Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2010;35(6):1279-89. doi:10.1038/npp.2009.230.
95. Utge SJ, Soronen P, Loukola A, Kronholm E, Ollila HM, Pirkola S et al. Systematic analysis of circadian genes in a population-based sample reveals association of TIMELESS with depression and sleep disturbance. PloS one. 2010;5(2):e9259. doi:10.1371/journal.pone.0009259.
96. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP et al. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(24):9950-5. doi:10.1073/pnas.1305814110.
97. McCarthy MJ, Wei H, Marnoy Z, Darvish RM, McPhie DL, Cohen BM et al. Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients. Translational psychiatry. 2013;3:e318. doi:10.1038/tp.2013.90.
98. Naylor E, Bergmann BM, Krauski K, Zee PC, Takahashi JS, Vitaterna MH et al. The circadian clock mutation alters sleep homeostasis in the mouse. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2000;20(21):8138-43.
99. Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V et al. Mania-like behavior induced by disruption of CLOCK. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(15):6406-11. doi:10.1073/pnas.0609625104.
100. Ozburn AR, Larson EB, Self DW, McClung CA. Cocaine self-administration behaviors in ClockDelta19 mice. Psychopharmacology. 2012;223(2):169-77. doi:10.1007/s00213-012-2704-2.
101. Abarca C, Albrecht U, Spanagel R. Cocaine sensitization and reward are under the influence of circadian genes and rhythm. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(13):9026-30. doi:10.1073/pnas.142039099.
102. Spencer S, Falcon E, Kumar J, Krishnan V, Mukherjee S, Birnbaum SG et al. Circadian genes Period 1 and Period 2 in the nucleus accumbens regulate anxiety-related behavior. The European journal of neuroscience. 2013;37(2):242-50. doi:10.1111/ejn.12010.
103. Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J et al. Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2008;147B(2):134-66. doi:10.1002/ajmg.b.30707.
104. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA : the journal of the American Medical Association. 1984;252(14):1905-7.
105. Mayfield RD, Harris RA, Schuckit MA. Genetic factors influencing alcohol dependence. British journal of pharmacology. 2008;154(2):275-87. doi:10.1038/bjp.2008.88.
106. Drummond SP, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. Alcoholism, clinical and experimental research. 1998;22(8):1796-802.
107. Wong MM, Brower KJ, Nigg JT, Zucker RA. Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. Alcoholism, clinical and experimental research. 2010;34(6):1033-44. doi:10.1111/j.1530-0277.2010.01178.x.
108. Wittmann M, Paulus M, Roenneberg T. Decreased psychological well-being in late 'chronotypes' is mediated by smoking and alcohol consumption. Substance use & misuse. 2010;45(1-2):15-30. doi:10.3109/10826080903498952.

109. Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. Addiction. 1994;89(4):455-62.
110. Gianoulakis C, Dai X, Thavundayil J, Brown T. Levels and circadian rhythmicity of plasma ACTH, cortisol, and beta-endorphin as a function of family history of alcoholism. Psychopharmacology. 2005;181(3):437-44. doi:10.1007/s00213-005-0129-x.
111. Garcia-Burgos D, Gonzalez F, Manrique T, Gallo M. Patterns of ethanol intake in preadolescent, adolescent, and adult Wistar rats under acquisition, maintenance, and relapse-like conditions. Alcoholism, clinical and experimental research. 2009;33(4):722-8. doi:10.1111/j.1530-0277.2008.00889.x.
112. Perreau-Lenz S, Zghoul T, de Fonseca FR, Spanagel R, Bilbao A. Circadian regulation of central ethanol sensitivity by the mPer2 gene. Addiction biology. 2009;14(3):253-9. doi:10.1111/j.1369-1600.2009.00165.x.
113. Dong L, Bilbao A, Laucht M, Henriksson R, Yakovleva T, Ridinger M et al. Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking. The American journal of psychiatry. 2011;168(10):1090-8. doi:10.1176/appi.ajp.2011.10111579.
114. Wang X, Mozhui K, Li Z, Mulligan MK, Ingels JF, Zhou X et al. A promoter polymorphism in the Per3 gene is associated with alcohol and stress response. Translational psychiatry. 2012;2:e73. doi:10.1038/tp.2011.71.
115. Hofstetter JR, Grahame NJ, Mayeda AR. Circadian activity rhythms in high-alcohol-preferring and low-alcohol-preferring mice. Alcohol. 2003;30(1):81-5.
116. Rosenwasser AM, Fecteau ME, Logan RW, Reed JD, Cotter SJ, Seggio JA. Circadian activity rhythms in selectively bred ethanol-preferring and nonpreferring rats. Alcohol. 2005;36(2):69-81. doi:10.1016/j.alcohol.2005.07.001.
117. Kovanen L, Saarikoski ST, Haukka J, Pirkola S, Aromaa A, Lonnqvist J et al. Circadian clock gene polymorphisms in alcohol use disorders and alcohol consumption. Alcohol Alcohol. 2010;45(4):303-11. doi:10.1093/alcalc/agq035.
118. Comasco E, Nordquist N, Gokturk C, Aslund C, Hallman J, Oreland L et al. The clock gene PER2 and sleep problems: association with alcohol consumption among Swedish adolescents. Upsala journal of medical sciences. 2010;115(1):41-8. doi:10.3109/03009731003597127.
119. Sjoholm LK, Kovanen L, Saarikoski ST, Schalling M, Lavebratt C, Partonen T. CLOCK is suggested to associate with comorbid alcohol use and depressive disorders. Journal of circadian rhythms. 2010;8:1. doi:10.1186/1740-3391-8-1.
120. McCarthy MJ, Fernandes M, Kranzler HR, Covault JM, Welsh DK. Circadian clock period inversely correlates with illness severity in cells from patients with alcohol use disorders. Alcoholism, clinical and experimental research. 2013;37(8):1304-10. doi:10.1111/acer.12106.
121. Perreau-Lenz S, Vengeliene V, Noori HR, Merlo-Pich EV, Corsi MA, Corti C et al. Inhibition of the casein-kinase-1-epsilon/delta/ prevents relapse-like alcohol drinking. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012;37(9):2121-31. doi:10.1038/npp.2012.62.
122. Arey R, McClung CA. An inhibitor of casein kinase 1 epsilon/delta partially normalizes the manic-like behaviors of the ClockDelta19 mouse. Behavioural pharmacology. 2012;23(4):392-6. doi:10.1097/FBP.0b013e32835651fd.
123. Kojetin DJ, Burris TP. REV-ERB and ROR nuclear receptors as drug targets. Nature reviews Drug discovery. 2014;13(3):197-216. doi:10.1038/nrd4100.
124. Hirota T, Lee JW, St John PC, Sawa M, Iwaisako K, Noguchi T et al. Identification of small molecule activators of cryptochrome. Science. 2012;337(6098):1094-7. doi:10.1126/science.1223710.
125. Jones KA, Hatori M, Mure LS, Bramley JR, Artymyshyn R, Hong SP et al. Small-molecule antagonists of melanopsin-mediated phototransduction. Nature chemical biology. 2013;9(10):630-5. doi:10.1038/nchembio.1333.